

## A Method of Preparing Memantine Hydrochloride

### Field of Invention

This invention relates to a synthesis method of Memantine Hydrochloride, which is a drug for the treatment of moderate to severe Alzheimer's disease (AD).

### Technical Background

Memantine Hydrochloride of Merz-Germany has come into the market since 1982 and is still used for treatment of Parkinson's disease, Neuropathic Myotonia and Dementia Syndrome with a trade name Akatinol in a few countries such as Germany now. It attracted great attention of clinic and market again when Memantine Hydrochloride was found to act as NMDA (N-methyl-D-aspartate) receptor antagonist. Now, Memantine Hydrochloride has been approved as an effective drug for the treatment of moderate to severe AD by the European Union and it has become the first approved drug for the treatment of moderate to severe AD. In USA, the phase III clinical study has been completed and NDA has been submitted to FDA. Since there hasn't been any effective medicine for the treatment of moderate to severe AD, Memantine Hydrochloride is in the highest flight in the field of dementia treatment now. Moreover, it has profound potentialities in acting as a medicine in the field of moderate to severe Vascular Dementia treatment, which has no effective clinic option; therefore, it is a great valuable clinical medicine and has a profound market potentiality.

With regard to the synthesis of Memantine Hydrochloride, there are two method reported in the literature, one is US patent 3391142 using acetonitrile / sulfuric acid and the other is US patent 4122193 using urea in the synthesis.

In the method of US patent 3391142, 1,3-dimethyl adamantane is bromized to yield 1-bromo-3,5-dimethyl adamantane, which is then subjected to acetylation and

ammonization in the presence of acetonitrile and sulfuric acid, extracted with benzene, dried and concentrated to yield 1-acetamino-3,5-dimethyl adamantane. After the alcoholysis with sodium hydroxide and diethylene glycol, extraction in benzene and concentration, memantine crude was obtained, which was then salified with hydrochloric acid, re-crystallize with ethanol/ether and purify to yield Memantine Hydrochloride.

This method uses acetonitrile, benzene and ether, which are hazardous to environment and human, in the process of acetylation, ammonization and re-crystallization. Furthermore, this method is difficult to hydrolyze acetyl compound, produces many by-products and darkens the product due to the reaction of long duration. The product purity is hard to meet the pharmaceutical use standard. Therefore, it is necessary to improve this method.

The method of US patent 4122193 uses 1-bromo-3,5-dimethyl adamantane as the raw material, which reacts with urea at 220°C in tube sealing to yield agglomerate product. The product is milled and mixed with water into mash, then acidified to adjust pH between 3 and 5. The impurity is removed by ether extraction. The aqueous layer is basified to a pH of between 12 and 13. After extracted with ether several times, the organic layers is combined, dried, salified by inletting HCl gas to yield Memantine Hydrochloride. This method adopts tube sealing, and the high reaction temperature may cause the agglomeration of product. It is, therefore, hard to industrialize.

#### Description of the Invention

This invention aims to develop a new preparation method of Memantine Hydrochloride to overcome the above-mentioned technical limitation and to provide a new process that facilitates the industrialization of this product.

The gist of this invention is as follows:

1-bromo-3,5-dimethyl adamantane is aminated with urea/formic acid, where formic acid is also used as solvent, hydrolyzed with inorganic acid aqueous solution, basified, extracted with solvent, and salified with hydrochloric acid. Then the target product Memantine Hydrochloride is collected.

The detailed preparation method involves the following steps:

1-bromo-3,5-dimethyl adamantane, urea and formic acid react at a molar ration of 1:0.5~10:1~15 at 50-180°C for 0.25-5h. After the reaction, inorganic acid aqueous solution is added. Hydrolyzation is performed at a pH from 1 to 3 at 50-100°C for 0.5 to 5h. The pH value of the solution is adjusted with inorganic acid aqueous solution to a pH from 10 to 14. After extracted with organic solvent, the extract is salified with hydrochloric acid. The target product Memantine Hydrochloride is collected. The yield can exceed 69.5% and the product purity can exceed 99.0%.

Based on this invention, the re-crystallization solvent can be used to re-crystallize the said salt to yield Memantine Hydrochloride.

The urea-formic acid act as the reaction reagent of amination and the said formic acid is anhydrous formic acid or formic acid aqueous solution of various concentrations. The formic acid is also used as solvent.

The molar ratio between 1-bromo-3,5-dimethyl adamantane and urea and formic acid is preferably 1:2~5:5~10 and the reaction temperature is preferably 60-150°C. The said inorganic acid may be one selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or their mixture.

The said inorganic base may be one selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or their mixture.

The organic solvent used for extraction may be one selected from hydrocarbon, ester,

ether or their mixture.

The said hydrocarbon includes benzene, toluene, xylene, cyclohexane, hexane, petroleum ether, etc.

The said ester includes ethyl acetate, butyl acetate, etc.

The said ether includes sulfuric ether, isopropyl ether, etc.

The re-crystallization solvent is preferably alcohol such as methanol, ethanol, propanol, isopropanol, butanol and tertiary butanol, ketone such as acetone and butanone, water and their mixture.

This invention provides a new preparation method that uses low-cost and facile raw materials, homogeneous phase and mild reaction conditions and simple post treatment, obtains high yield and high purity and is easy for mass production.

Using the method of this invention for preparing Memantine Hydrochloride brings the following advantages:

1. This invention makes some improvement based on the literature's method, such as adding formic acid to the mixture of 1-bromo-3,5-dimethyl adamantane and urea so that the reaction can be completed at a lower temperature and there is no need of tube sealing. The product is homogenous without agglomerations and easy for post treatment. It has overcome the difficulty for industrialization and created an advantage for mass production.
2. Due to the presence of formic acid in the aminating reaction, the product of 3,5-dimethyl adamantane is protected in the form of methanamide to avoid oxidization, and the reaction solution maintains light color. After the hydrolysis and salification, the purity of the yielded Memantine Hydrochloride crude can reach 99.0% and that of the re-crystallized product can reach 99.98% (see Fig.1). The yield is 69.5% and the melting point is 332°C (DSC), which is reported by 290-295°C in the literature.

Description of the drawing

Fig.1 is the GC spectrum of purified Memantine Hydrochloride.

Embodiments

**Example 1**

To 100g of 1-bromo-3,5-dimethyl adamantane and 86g of urea, adding 80ml of 80wt% formic acid, heating to 80°C and holding for 3 hours. Cooling to the room temperature and adding 95ml of concentrated hydrochloric acid to hydrolyze at 80°C for about 1 hour. Adjusting with 30% sodium hydroxide to a pH of 12, extracting with toluene twice, combining the organic layers and washing with water. Concentrating under reduced pressure to yield a limpid yellow solution as the 1-amino-3,5-dimethyl adamantane crude. To the crude, adding 150ml of ethanol and concentrated hydrochloric acid, heating to dissolve and crystallizing to yield white solid. Drying the solid and re-crystallizing with ethanol to yield 61.0g of pure Memantine Hydrochloride. The yield of product is 68.8% (GC 99.5%).

<sup>1</sup>HNMR (CDCl<sub>3</sub>, 400MHZ): 80.833 (6H, singlet), 1.156 (2H, quartet), 1.328 (4H, quartet), 1.683 (4H, quartet), 1.869 (2H, broad signal), 2.179 (1H, broad signal), 8.28(3H, broad signal).

MS (Q-Tof micro, ESI+): 179(M<sup>+</sup>), 164, 122, 108, 93 and 55.

Element Analysis (C<sub>12</sub>H<sub>21</sub>N.HCl): actual results (calculated value%): C 66.77(66.80), H 10.40(10.28), N 6.48(6.49), Cl 16.39(16.43)

**Example 2**

To 100g of 1-bromo-3, 5-dimethyl adamantane and 86g of urea, adding 72ml of 94wt% formic acid, heating to 120°C and holding for 2 hours. Cooling to the room temperature and adding 385ml of 10% hydrochloric acid to hydrolyze at 100°C for about 1 hour. Adjusting with 30% sodium hydroxide solution to a pH of 12, extracting with butyl acetate twice, combining the organic layers and washing with water. Concentrating under reduced pressure to yield a limpid yellow solution as

1-amino-3,5-dimethyl adamantane crude. To the crude, adding 150ml of ethanol and concentrated hydrochloric acid, heating to dissolve and crystallizing to yield white solid. Drying the solid and re-crystallizing with water to yield 60.4g of pure Memantine Hydrochloride. The yield is 68.1% (GC 99.1%).

**Example 3**

To 100g of 1-bromo-3, 5-dimethyl adamantane and 110g of urea, adding 60ml of anhydrous formic acid, heating to 150°C and hold for 1 hour. Cooling to the room temperature and adding 95ml of concentrated hydrochloric acid to hydrolyze at 100°C for 1 hour. Adjusting with 30% sodium hydroxide solution until the solution becomes basic. Extracting with toluene twice, combining the organic layers and washing with water. Concentrating under reduced pressure to yield a limpid yellow solution as 1-amino-3,5-dimethyl adamantane crude. To the crude, adding 150ml of ethanol and concentrated hydrochloric acid, heating to dissolve and crystallizing to yield white solid. Drying the solid and re-crystallizing with acetone to yield 61.7g of pure Memantine Hydrochloride. The yield is 69.5% (GC 99.9%).

**Example 4**

To 100g of 1-bromo-3, 5-dimethyl adamantane and 86g of urea, adding 80ml of 80wt% formic acid, heating to 80°C and holding for 3 hours. Cooling to the room temperature and adding 75ml of 85% phosphoric acid to hydrolyze at 80°C for 1 hour. Adjusting with 10% potassium hydroxide aqueous solution to a pH of 12. Extracting with toluene twice, combining the organic layers and washing with water. Concentrating under reduced pressure to yield a limpid yellow solution as 1-amino-3,5-dimethyl adamantane crude. To the crude, adding 150ml of ethanol and concentrated hydrochloric acid, heating to dissolve and crystallizing to yield a white solid. Drying the solid and re-crystallizing with ethanol to yield 61.0g of pure Memantine Hydrochloride. The yield is 68.8% (GC 99.5%).

<sup>1</sup>HNMR (CDCl<sub>3</sub>, 400MHZ): 80.833 (6H, singlet), 1.156 (2H, quartet), 1.328 (4H, quartet), 1.683(4H, quartet), 1.869 (2H, broad signal),

2.179 (1H, broad signal), 8.28 (3H, broad signal).

MS (Q-Tof micro, ESI+): 179(M<sup>+</sup>), 164, 122, 108, 93 and 55.

Element Analysis (C<sub>12</sub>H<sub>21</sub>N.HCl): actual results (calculated value%): C 66.77 (66.80), H 10.40 (10.28), N 6.48(6.49) and Cl 16.39(16.43)